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## **Is there a future for small molecule drugs in the treatment of rheumatic diseases?**

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**Abstract:** PURPOSE OF REVIEW: In this review, we outline the landscape of recent developments regarding small molecule compounds for the treatment of inflammatory disorders by discussing drug candidates currently in the pipeline. We also stress the fact that novel techniques are available to evaluate the safety of new therapeutics at an early stage of development. **RECENT FINDINGS:** Regulation of signal transduction has evolved into an important field of drug research, and small molecule inhibitors of a number of pathways are tested as new anti-inflammatory agents. For rheumatic diseases, specific Jak3 and Syk inhibitors are, so far, the most successful compounds due to their good efficacy, representing a significant advantage over p38 mitogen-activated protein kinase inhibitors. Additional benefit in the treatment of inflammatory diseases may be provided by targeting CD80, IL-12/IL-23, AP-1 transcription factor and receptors modulating cellular activation like chemokine receptors, Toll-like receptors and adenosine A3 receptor. **SUMMARY:** There is a big hope that novel small molecule drugs, which are rationally designed, based on scientific advancements and biotechnological improvements, will achieve or even exceed efficacy of protein drugs. Thereby, new therapeutic alternatives would be given, and chances for improved outcomes in the care of rheumatic patients provided.

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# Is there a future for small molecule drugs in the treatment of rheumatic diseases?

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## Purpose of review

In this review, we outline the landscape of recent developments regarding small molecule compounds for the treatment of inflammatory disorders by discussing drug candidates currently in the pipeline. We also stress the fact that novel techniques are available to evaluate the safety of new therapeutics at an early stage of development.

## Recent findings

Regulation of signal transduction has evolved into an important field of drug research, and small molecule inhibitors of a number of pathways are tested as new anti-inflammatory agents. For rheumatic diseases, specific Jak3 and Syk inhibitors are, so far, the most successful compounds due to their good efficacy, representing a significant advantage over p38 mitogen-activated protein kinase inhibitors. Additional benefit in the treatment of inflammatory diseases may be provided by targeting CD80, IL-12/IL-23, AP-1 transcription factor and receptors modulating cellular activation like chemokine receptors, Toll-like receptors and adenosine A3 receptor.

## Summary

There is a big hope that novel small molecule drugs, which are rationally designed, based on scientific advancements and biotechnological improvements, will achieve or even exceed efficacy of protein drugs. Thereby, new therapeutic alternatives would be given, and chances for improved outcomes in the care of rheumatic patients provided.

## Keywords

inflammation, rheumatoid arthritis, small molecule

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## Introduction

The remarkable advance and benefit of biologics, foremost antitumour necrosis factor (TNF) therapeutics, in the control of disease activity and joint destruction in patients with rheumatic disorders is indisputable. It is, however, also apparent that these drugs fail to achieve an American College of Rheumatology (ACR) 70 response in about 40% of the patients with rheumatoid arthritis (RA). Moreover, primary or secondary resistance to biological therapy represents a substantial complication in a significant group of patients. Thus, there is still an unmet therapeutic need in the management of inflammatory autoimmune diseases and drug development research is actively seeking new solutions [1<sup>••</sup>,2].

Small molecules are low molecular weight (<1 kDa) compounds that have a potent biological effect. Small molecules typically bind to cellular structures such as surface receptors, intracellular signalling proteins and enzymes with subsequent modulation of their function. Most of the commonly used drugs, including disease modifying antirheumatic drugs (DMARDs), are small

molecules. For drug development, small molecules provide a significant advantage due to the fact that a wide range of these compounds can be synthesized in a relatively short period of time and can be easily screened for specificity and capacity of binding with a target. In addition, in contrast to biologicals, small molecules are orally bioavailable and their manufacturing is cost-effective, which is an important advantage for patients and healthcare systems. For these reasons, there is a constant substantial interest in novel small molecules for the treatment of rheumatic disorders, and more than half of the new anti-inflammatory therapeutics currently tested in preclinical and clinical phases are small molecules. The idea behind this effort is the development of an oral cytokine inhibitor being equally or more effective than biological drugs but having all the advantages of small molecules.

In the current review, we aim to update on the recent advances in the field of small molecule research for the treatment of rheumatic conditions and to assess the prospects of novel small molecules to enter clinical use (Table 1). We also emphasize that novel approaches are

**Table 1 Small molecule compounds under clinical development for rheumatic conditions**

Target	Target function	Drug candidates	Disease	Status
Jak Syk	Cytokine signalling Immunoreceptor signalling, cytokine production	CP-690 550, INCB18424 Tamatinib fosdium	RA, psoriasis, CD RA, allergic asthma	Phase II, I Phase II
p38 MAPK PDGFR, c-kit, ABL kinases	Cytokine production, matrix degradation Fibrosis, pannus formation, cytokine production	VX-702, ARRY-797 Imatinib mesylate	RA, psoriasis, CD SSc, PAH, RA, spondyloarthropaties	Phase II, I Phase II
IL-12/23 CD80 CCR5	Th1-dependent immune response T cell activation Cell recruitment	Apilimod mesylate RhuDex Maraviroc	CD, RA RA RA, HIV infection	Phase II Phase II Phase II

CD, Crohn's disease; MAPK, mitogen-activated protein kinase; PAH, pulmonary arterial hypertension; RA, rheumatoid arthritis; SSc, systemic sclerosis.

needed to evaluate the tolerability of new drugs at an early stage of development.

### Inhibition of tyrosine kinases

Most important for the effectiveness of small molecule therapeutics are the identification and targeting of molecular pathways and molecules that play a key role in the development of the disease. Thus, comprehension of intracellular signalling pathways, which govern initiation and maintenance of inflammation, is a prerequisite for rational design of novel pharmacologicals aiming at combating excessive immune activation. The last decade of ongoing intensive research in this field provided deep insights into the molecular basis of inflammatory disorders [3<sup>••</sup>], paving the way for the development of signal transduction therapy into one of the most important areas of drug research [4].

There are some examples of successful application of therapeutics targeting signal transduction in clinical medicine. Imatinib mesylate- a potent inhibitor of tyrosine kinases, including platelet-derived growth factor (PDGF) receptor, c-Kit and c-Abl related kinases- is an established treatment for chronic myeloid leukaemia and gastrointestinal stromal tumours. As c-Abl has been recently identified as an important molecule in the transforming growth factor (TGF)- $\beta$  signalling [5], it was suggested that imatinib through dual inhibition of PDGF and TGF- $\beta$  might inhibit fibrosis- a condition that cannot be successfully approached by any known treatment so far. As demonstrated by Distler *et al.* [6<sup>••</sup>] imatinib mesylate has a potent dose-dependent antifibrotic effect *in vitro* in dermal fibroblasts and *in vivo* in bleomycin-induced experimental dermal fibrosis, without evidence of toxic side effects. The first results of currently ongoing clinical trials evaluating efficacy and safety of imatinib mesylate in patients with severe cutaneous scleroderma or systemic sclerosis (SSc) with severe cutaneous involvement are awaited. In addition to imatinib, the novel tyrosine kinase inhibitors, nilotinib and dasatinib, have emerged as highly promising therapeutic agents against fibrosis in patients with SSc [7]. Interestingly, imatinib mesylate and other

small molecule tyrosine kinase inhibitors proved to be beneficial in refractory cases of other inflammatory diseases, particularly characterized by increased proliferation of fibroblasts, like RA [8].

The nonreceptor tyrosine kinase Janus kinase 3 (Jak3) and signal transducer and activator of transcription (Stat) are crucial for transmitting signals from a common  $\gamma$  chain of a number of receptors for cytokines, including INF- $\gamma$ , IL-6, IL-2, IL-4, IL-7, IL-12 and IL-15. All of these have been shown to be implicated in the pathogenesis of RA. Therefore, intervening with the activation of this pathway might represent an alternative approach to suppress synovial inflammation and disease activity [9]. Interestingly, expression of Jak3, Stat1, Stat4 and Stat6 in RA synovium decreases in response to standard treatment with conventional DMARDs [10]. Moreover, as expression of Jak3 is restricted to immune cells, the risk for off-target side effects appears reduced, which might be an advantage over inhibitors of p38 mitogen-activated protein kinase (MAPK).

Recently, selective inhibitors of Jak were suggested as potential novel anti-inflammatory treatment for RA and psoriasis. For the treatment of arthritis, CP-690 550- a selective inhibitor of Jak3 (Pfizer; New York City, New York, USA)- is a leading compound in clinical phases of development. Initially designed as an immunosuppressive agent for application in organ transplants, CP-690 550 turned out to have a potent anti-inflammatory effect and, at the same time, a relatively favourable safety profile [11]. A dose ranging phase II clinical trial [12] in 264 patients, who were resistant to methotrexate (MTX) and biologics, showed the best reported results so far for a small molecule tested in RA. CP-690 550 applied over 6 weeks in three increasing dosages proved to be superior to placebo in all study arms. The ACR response criteria were met in 70–81% for ACR20, 33–54% for ACR50 and in 13–28% for ACR70. Respective values for a placebo group were the following: ACR20 29%, ACR50 6% and ACR70 3%. Currently, another 6-month long phase II study assessing efficacy and safety of CP-690 550 in patients with RA is ongoing.

Another Jak inhibitor under preclinical development is INCB18424 (Incyte Corporation; Wilmington, Delaware, USA). Its efficacy has been demonstrated in rodent models of arthritis, and a phase I trial in healthy volunteers is under way [13].

Spleen tyrosine kinase (Syk), belonging to intracellular tyrosine kinases, is a key molecule in the signalling from immunoreceptors such as Fc receptor and B-cell receptor [14]. Moreover, Syk has been shown to be constitutively expressed in RA synovial fibroblasts, and its activation by IL-1 $\beta$  and TNF- $\alpha$  in turn initiates MAPK cascade [15]. In a recently completed phase II clinical trial involving 189 patients with RA, the oral Syk inhibitor R788 (tamtinib fosdium; Rigel Pharmaceuticals, San Francisco, California, USA) showed statistically significant improvements in ACR20, ACR50, ACR70 and DAS28 and a good tolerability was demonstrated.

### **Inhibition of p38 mitogen-activated protein kinase pathway**

The p38 MAPK signalling cascade has a prominent role in the development of inflammation by mediating cellular response to stress, pathogens and cytokines. Hyperactivation of p38 MAPK, along with resultant overproduction of IL-1 $\beta$  and TNF- $\alpha$ , is a hallmark of inflammatory disorders, such as RA, spondylarthropathies, inflammatory bowel disease and psoriasis [16<sup>•</sup>]. As components of the p38 MAPK pathway converge various stimulatory signals and mediate expression of numerous genes, from a molecular perspective, they appear as promising targets for anti-inflammatory interventions [17]. It is, however, important to note that not more than one-third of TNF- $\alpha$ -induced genes in synovial fibroblasts of patients with RA are p38 MAPK dependent [18<sup>••</sup>]. In addition, as a major induction of TNF- $\alpha$  *in vivo* is mediated by Toll-like receptors (TLRs) [19], which only in part signal through p38 MAPK, TNF- $\alpha$  appears to be above the major induction of p38. These observations point to the notion that inhibition of p38 might not achieve the excellent results observed for the blockade of TNF- $\alpha$ .

Early p38 MAPK inhibitors showed only limited success, primarily due to their undesired pharmacological inhibition of physiologically important kinases and consequent dose-dependent toxicities (liver and central nervous system toxicity, impaired host defence) [20]. Therefore, selective inhibition of p38 in activated immune cells and preservation of the regulatory role of p38 kinases have been the major challenges for novel p38 inhibitors. Currently, new generations of p38 MAPK inhibitors, optimised in terms of specificity and potency, are entering preclinical and clinical trials. One of the leading compounds is VX-702 (Vertex Pharmaceuticals, Cambridge, Massachusetts, USA). A phase II clinical trial

of VX-702 has been completed in patients with moderate to severe RA, demonstrating its good tolerance and improvement in ACR20. Another p38 MAPK inhibitor, ARRY-797 (Array Biopharma, Boulder, Colorado, USA)- a selective and potent inhibitor of p38 $\alpha$ - is currently in preclinical development. This compound has proved to be very effective in reducing the production of IL-6 and TNF- $\alpha$  in rats challenged with lipopolysaccharide (LPS). Furthermore, signs of inflammation and histopathological changes of adjuvant-induced arthritis (AIA) were ameliorated [21]. Recently, ARRY-797 has advanced into clinical trials to study its safety and efficacy in patients.

Another pathway closely related to p38 MAPK is the MAPK kinase/extracellular signal-regulated kinase (MEK/ERK) signalling cascade. This pathway is activated in inflammatory conditions and has a role in increased production of TNF- $\alpha$  and IL-1 $\beta$ . ARRY-162 (Array Biopharma), another upcoming small molecule, selectively inhibits MEK-1/2. Previously shown to be efficacious in AIA and collagen-induced arthritis (CIA), this compound entered trials in healthy volunteers, demonstrating good tolerability. Its inhibition of the MEK/ERK pathway was assessed in ex-vivo measurements of the production of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 by whole blood cells under stimulatory conditions. Clinical evaluation of ARRY-162, in combination with MTX, in patients with RA is ongoing [22].

### **Inhibition of transcription factors**

Transcription factors bridge the interaction between active receptors and transcriptional response in the nucleus. Having this central function in cell activation, they represent interesting targets for small molecules. Activator protein-1 (AP-1) is a downstream target of p38 MAPK and c-Jun activated kinase (JNK) in response to cytokines and cellular stress.

T-5224- a novel c-Fos/AP-1 inhibitor (Toyama Chemical, Tokyo, Japan)- shows good promise as a new drug for treatment of arthritis. T-5224 was demonstrated to prevent joint destruction, pannus formation and osteoclastogenesis in CIA in rats. This effect was partially dependent on the reduction of IL-1 $\beta$  and matrix metalloproteinase 3 (MMP-3) production [23]. A phase I clinical trial of this interesting small molecule candidate has been initiated.

### **Small molecule inhibitor of IL-12/IL-23**

IL-12 induces differentiation of naive T helper cells into T helper cell type 1 (Th1) and is central to the pathogenesis of Th1-mediated immunologic disorders. IL-23 shares the p40 protein subunit with IL-12 and plays a critical role in the generation of effector T cells and IL-17 producing T cells. Apilimod mesylate (STA-5326;

Synta Pharmaceuticals, Lexington, Massachusetts, USA) is a novel oral small molecule inhibitor of IL-12/23. This compound selectively inhibits production of IL-12/IL-23 through inhibition of nuclear translocation of c-Rel and transcriptional inhibition of both IL-12 p35 and IL-12/IL-23 p40 [24]. Preclinical studies [25<sup>\*</sup>] of STA-5326 demonstrated successful IL-12/IL-23 inhibition and suppression of Th1-dependent immune response. In the murine model of inflammatory bowel disease, STA-5326 inhibited the production of IFN- $\gamma$  and the development of histopathologic changes in the colon, suggesting potential benefit of this compound for the treatment of Th1-dependent autoimmune inflammatory diseases. So far the drug was demonstrated to be efficacious in patients with active, moderate to severe Crohn's disease, as assessed by reduction of the Crohn's disease activity index (CDAI) at day 28 of treatment [26]. Currently, the drug is being evaluated in patients with RA in a phase II clinical trial.

### Small molecule interacting with cell surface receptors

An interesting protein that emerges as a new therapeutic target in RA is A3 adenosine receptor (A3AR)- a Gi protein associated cell-surface receptor. A3AR is highly expressed on mononuclear cells in inflammatory conditions but has low expression in normal tissue [27]. Adenosine exerts anti-inflammatory effects by activation of A3AR and downregulation of NF- $\kappa$ B signalling, resulting in decrease of TNF- $\beta$  release and inhibition of proliferation of T cells [28]. Interestingly, release of adenosine partly accounts for the immunomodulatory action of MTX. CF101 (Can-Fite BioPharma, Lexington, Massachusetts, USA) is a novel highly selective A3AR agonist. Recently published data from the phase II clinical trial evaluating CF101 in 74 patients with RA demonstrated that therapy with CF101 over 12 weeks is well tolerated and improves signs and symptoms of arthritis, although statistical significance was not reached. A double-blind randomized placebo-controlled study [29], aimed at a definite evaluation of the benefit of modulation of A3AR in RA, is currently ongoing.

As synovial inflammation is dependent on the influx and retention of inflammatory cells, therapies targeting chemokine receptors could represent a novel approach to control chronic inflammation [30]. Some proofs of concept studies are ongoing. Maraviroc (Pfizer), an oral selective reversible antagonist of CCR5, of which RANTES (regulated upon activation, normal T cell expressed and secreted) is the major natural ligand, was recently approved by the Food and Drug Administration (FDA) for treatment of HIV infection and is currently tested in patients with RA. A phase II clinical trial [31] is being

conducted to assess its safety and efficacy. At the same time, another small molecule, MLN3897 (Millenium Pharmaceuticals, Cambridge, Massachusetts, USA), an inhibitor of CCR1, a chemokine receptor mostly expressed on macrophages, failed to demonstrate improvement at ACR20 in a phase II clinical trial in RA.

As costimulatory signals provided by CD80-CD28 interaction are necessary to fully activate T cells upon TCR stimulation, CD80-CD28 interaction plays a critical role in regulating T cell activation and is implicated in the pathogenesis of autoimmunity. Recently, compounds that selectively block binding of CD80 to CD28 have been discovered and were shown to inhibit this interaction with high potency. RhuDex (Active Biotech, Lund, Sweden)- an orally available CD80 antagonist- is currently in phase II clinical evaluation in RA [32].

Due to their critical function in linking innate and adaptive immunity and their proinflammatory properties, disease associated TLRs are appealing targets for pharmacologic intervention [33<sup>\*</sup>]. 2'-O-Methyl-modified RNAs, acting as TLR7 antagonists, are able to significantly reduce the production of IFN- $\gamma$  and IL-6 in human peripheral blood mononuclear cells (PBMCs) and in mice *in vivo*. Therefore, their potential utility in the treatment of autoimmune diseases that involves TLR7 stimulation like systemic lupus erythematosus (SLE) has been suggested [34]. Another molecule that has been recently demonstrated to provide therapeutic benefit by engaging with TLR4 is Chaperonin 10 (Cpn 10)- a heat shock protein. Cpn10 administered intravenously is well tolerated and efficacious as proved by phase II double-blind randomized trials in RA, psoriasis and multiple sclerosis [35].

### Efficacy and safety considerations

In order to provide an advance for rheumatic patients, novel small molecules have to reach or exceed efficacy and safety observed for biologics. The high rate of withdrawals from the drug development process observed so far for small molecule compounds indicates the existence of numerous obstacles in the transition from the drug discovery phase into the early development and finally into clinical application. Inefficacy or high toxicity is the most common reason for failures. Therefore, it is apparent that major and constant efforts are needed to overcome these problems. For instance, high-throughput technologies such as gene arrays can be applied to improve the drug development process [36]. Thereby, measurements of changes in gene expression after treatment in target cell populations can give information about the intended target effects as well as about undesired off-target properties of a drug. In addition, other factors, like elaboration of clear guidelines regarding

animal models assuring good translation of preclinical data on clinical efficacy [37<sup>•</sup>], good characterization of patient cohorts as well as use of pharmacogenomics for better prediction of patients who can benefit the most from a given drug [38], might substantially augment chances for successful development of novel oral anti-inflammatory modalities. It also seems to be of crucial importance to identify windows of opportunity during disease progression, in which a given small molecule drug is most beneficial.

## Conclusion

The successful application of small molecule kinase inhibitors in oncology provides a tremendous insight into the signal transduction therapy and creates a foundation for the extension of the application of small molecules to rheumatology. As outlined in the overview, there are currently a significant number of small molecule drugs in the pipeline for treatment of inflammatory diseases, with some promising molecules such as Jak-Stat and Syk inhibitors on the horizon. At the same time, technological advances, like systematic screening for new small molecule compounds and evaluation of potency and specificity of their interaction with a target structure, create new possibilities for the development of even more novel small molecules [39].

As the blockade of TNF- $\alpha$  leads to a remarkable improvement in the ACR response, which cannot be achieved by any tested small molecular drug so far, it is tempting to speculate that oral inhibitors of TNF- $\alpha$  would be a groundbreaking invention in the therapy of rheumatic diseases. This undoubtedly remains an enormous challenge for the drug industry. In disease conditions, a number of signalling pathways contribute to the activation of TNF- $\alpha$ , explaining why no single kinase inhibitor can equal the efficacy of anti-TNF agents. On the other hand, the fact that even with anti-TNF- $\alpha$  biologics at the most 60% of patients achieve an ACR70 response implicates that a considerable part of disease-relevant mechanisms are not addressed by currently available drugs. This indicates a big potential of continued research focusing on cells that have not been directly targeted so far, like, for example, synovial fibroblasts [40<sup>•</sup>]. Moreover, recent scientific advances raise a possibility of molecular disturbances on the level of microRNAome and epigenome, which might require completely new therapeutic solutions [41<sup>••</sup>].

## Acknowledgement

The information on the current status of drugs discussed in the review is based on the information obtained from the public database of clinical trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) or from the Internet resources of pharmaceutical companies.

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